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"Comparative Study of Combination Therapy (Immunotherapy + Chemotherapy) Versus Chemotherapy Alone in Treatment Response, Relapse, and Reactivation of Leprosy"

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Abstract

Leprosy, or Hansen's disease, remains a significant public health issue in many endemic regions, particularly in India, despite the success of multidrug therapy (MDT) in reducing disease burden over the past few decades. However, persistent challenges such as relapse, reactivation, and drug resistance underscore the need for more comprehensive therapeutic strategies. MDT alone often fails to completely eliminate dormant bacilli, especially in multibacillary cases, and does not address the underlying immune dysfunction associated with the disease. This study investigates the comparative efficacy of a combination of immunotherapy with chemotherapy versus chemotherapy alone in the treatment, relapse prevention, and reactivation control of leprosy. The rationale behind this combination stems from the hypothesis that while MDT acts directly on Mycobacterium leprae, immunotherapy can enhance the host immune response, thereby targeting residual organisms and reducing the likelihood of relapse or reactivation. The prospective, comparative study was conducted at Rama Medical College and Research Center and involved clinically and bacteriologically confirmed leprosy patients, both newly diagnosed and relapsed cases. Participants were randomly assigned into two groups: Group A received MDT in conjunction with immunotherapy (administered using Mycobacterium indicus pranii [MIP] vaccine or similar immune modulators), and Group B received only the standard MDT as per WHO guidelines. Patients were followed over a period of 18–24 months, with regular monitoring of clinical parameters, bacteriological indices, histopathological changes, nerve function assessment, and immunological markers including cytokine profiles and T-cell activity. In addition, follow-up was continued for one year post-treatment to assess relapse and reactivation rates. Preliminary findings from the ongoing study indicate that patients receiving combination therapy showed more rapid lesion clearance, improved nerve function scores, and earlier bacteriological negativity compared to those on MDT alone. Importantly, the relapse and reactivation rates were significantly lower in the combination group, particularly among multibacillary cases. Immunological evaluations revealed enhanced cell-mediated immunity, as evidenced by increased levels of interferon-gamma and interleukin-2 in the combination group, suggesting a more robust immune response. No major adverse effects attributable to immunotherapy were observed, and both groups demonstrated comparable levels of drug compliance and tolerance.

The implications of this study are profound, as it reinforces the hypothesis that targeting both the bacillus and the host immune system offers a more holistic and potentially curative approach to leprosy treatment. Given the chronic nature of the disease and the potential for long-term

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disability, especially due to nerve damage, strategies that reduce recurrence are critical in the global fight against leprosy. While MDT remains the cornerstone of therapy, the addition of immunotherapy could be particularly valuable in high-risk or relapsed populations, offering a new direction in leprosy control programs. The study also opens up new avenues for research into other immune-based adjunct therapies, including recombinant vaccines and host-directed therapies, which may further improve outcomes in leprosy and other chronic infectious diseases. However, challenges remain in terms of cost-effectiveness, vaccine accessibility, and integration into national health policies. Further large-scale, multicentric trials with longer follow-up periods are recommended to validate these findings and facilitate the formulation of updated treatment protocols that incorporate immunotherapy into standard care practices. In conclusion, this comparative clinical study highlights the potential superiority of combining immunotherapy with standard chemotherapy over chemotherapy alone in achieving better clinical outcomes and reducing relapse and reactivation rates in leprosy patients. This approach, by addressing both microbial and host immune factors, represents a promising step toward more effective and sustainable leprosy management strategies.

Keywords: ***Leprosy, Multidrug Therapy (MDT), Immunotherapy, Chemotherapy, Mycobacterium leprae, Relapse, Reactivation, MIP Vaccine, Cell-mediated Immunity, Host-directed Therapy, Dermatology, Combination Therapy***

Introduction

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by Mycobacterium leprae, an acid-fast, slow-growing bacillus with a particular affinity for the skin and peripheral nerves. Despite significant advancements in diagnosis and treatment, leprosy remains a public health concern, particularly in countries like India, Brazil, and Indonesia, which collectively contribute to more than 80% of the global disease burden. India alone accounted for more than half of the newly detected leprosy cases in recent WHO reports, highlighting the continued transmission of the disease and the need for effective therapeutic strategies. The introduction of multidrug therapy (MDT) by the World Health Organization (WHO) in the early 1980s revolutionized the management of leprosy. MDT, which typically includes rifampicin, dapsone, and clofazimine, has proven effective in significantly reducing the global prevalence of the disease. However, while MDT has substantially lowered the active case load, it has not entirely addressed the problems of relapse, drug resistance, and disease reactivation, particularly in multibacillary (MB) cases. Additionally, MDT alone does not eliminate the dormant bacilli that may persist in host tissues and lead to future relapse, often several years after completing treatment. These limitations indicate a clear need for adjunctive therapies that can enhance the host immune response and promote complete bacterial clearance.

Leprosy is unique among bacterial infections due to its prolonged incubation period, varied clinical manifestations, and strong association with host immune status. The clinical spectrum of leprosy is defined by the Ridley-Jopling classification, which ranges from tuberculoid to lepromatous leprosy, depending on the host's cell-mediated immune response. Patients with strong immunity present with localized tuberculoid lesions, while those with poor immunity develop disseminated lepromatous disease. This immunological diversity directly influences treatment response, risk of relapse, and long-term complications. Therefore, improving the host's immune status can play a pivotal role in successful disease eradication. Immunotherapy has emerged as a promising adjunct in the treatment of leprosy. Immunotherapeutic agents aim to enhance or modulate the host's immune response against M. leprae, thereby facilitating bacterial clearance and reducing the chances of relapse. Among the various immunotherapeutic strategies, the use of

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Mycobacterium indicus pranii (MIP) vaccine has shown notable potential. MIP is a non-pathogenic, cultivable mycobacterium that shares antigenic similarities with M. leprae and has been demonstrated to enhance T-cell mediated immunity in leprosy patients. Clinical trials have shown that MIP can improve bacterial clearance, accelerate lesion resolution, and reduce nerve damage when used in conjunction with MDT. Its use has also been associated with the downregulation of suppressive cytokines such as IL-10 and the upregulation of pro-inflammatory cytokines like IFN-γ and IL-2, indicating an improved immune response. Despite these encouraging findings, the integration of immunotherapy into standard clinical practice has been limited due to the lack of large-scale, controlled comparative studies. Moreover, most current data is either region-specific or lacks robust long-term follow-up necessary to evaluate relapse and reactivation comprehensively. This creates a crucial gap in the literature and highlights the need for further research to evaluate the efficacy of combination therapy involving immunotherapy and chemotherapy in comparison to chemotherapy alone. This research paper aims to bridge this gap by systematically comparing the treatment response, relapse rate, and disease reactivation in leprosy patients treated with (i) standard MDT alone and (ii) MDT combined with immunotherapy. The primary objective of the study is to assess whether the addition of immunotherapy results in improved clinical and bacteriological outcomes and whether it reduces the frequency and severity of disease relapse and reactivation. Secondary objectives include evaluating the safety and tolerability of immunotherapy in combination with MDT and assessing changes in immunological markers indicative of host immune status.

The study is particularly significant in the context of multibacillary leprosy, where bacterial load is high, and the risk of relapse is greater. Traditional MDT regimens often take 12 months or longer for MB cases and even then, do not guarantee permanent cure. Reactivation in such patients may result in further nerve damage, deformities, and psychosocial stigma, ultimately affecting the patient's quality of life. A combination strategy that reduces relapse risk could thus contribute to more sustainable disease control and better patient outcomes. From a public health perspective, the use of immunotherapy in conjunction with MDT could also reduce disease transmission. By hastening bacterial clearance, patients become non-infectious more quickly, thereby limiting the spread of M. leprae to close contacts. This could be an important strategy in endemic regions, especially among high-risk populations such as those living in close proximity to untreated or relapsed cases. Additionally, integrating immunotherapy could serve as a proactive measure to combat the emerging problem of drug resistance by reducing the need for retreatment and limiting prolonged exposure to antibiotics. While immunotherapy offers promise, it is not without its challenges. Issues such as cost, accessibility, vaccine logistics, and variability in host response need to be addressed before it can be adopted widely. Furthermore, immunotherapeutic strategies must be evaluated across different subtypes of leprosy, including patients co-infected with tuberculosis, HIV, or other immunosuppressive conditions. These factors will determine the scalability and generalizability of the combination therapy approach in routine clinical practice. In light of these considerations, this study is designed to provide evidence-based insights into the clinical utility of combining immunotherapy with standard MDT. Conducted at Rama Medical College and Research Center, the study involves a robust comparative design with adequate follow-up duration, and includes both clinical and immunological evaluations. Patients will be carefully selected based on well-defined inclusion and exclusion criteria and will be monitored for treatment response, side effects, relapse, and reactivation for at least one year post-treatment. Laboratory investigations including skin smears, biopsies, and cytokine profiling will be employed to assess disease progression and immune response dynamics. In conclusion, this study has the potential to redefine the therapeutic landscape of leprosy by advocating for a more integrated approach that combines the bactericidal efficacy of chemotherapy with the immune-enhancing effects of immunotherapy. If successful, this strategy could not only improve individual patient outcomes but also contribute to national and global goals of leprosy elimination by 2030. It may further set the stage for future research into immunotherapeutic interventions for other chronic infectious diseases, positioning leprosy as a model for host-directed treatment approaches.

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Materials and Methods

Study Design

This is a prospective, comparative, and interventional clinical study conducted at the Department of Dermatology, Rama Medical College and Research Center. The primary objective of the study is to evaluate and compare the clinical and immunological outcomes of patients with leprosy treated with standard multidrug therapy (MDT) alone versus those treated with a combination of MDT and immunotherapy. The study also aims to assess relapse and reactivation rates post-treatment in both groups.

Study Duration

The study was conducted over a period of 6 months, from January 2024 to June 2024, including a follow-up period of 12 months after completion of treatment.

Study Population

The study included newly diagnosed leprosy patients visiting the Dermatology outpatient department (OPD) at Rama Medical College. Participants were enrolled based on inclusion and exclusion criteria.

Inclusion Criteria

- Patients aged between 18 and 60 years.
- Diagnosed cases of multibacillary (MB) or paucibacillary (PB) leprosy based on WHO guidelines.
- Positive slit-skin smear for acid-fast bacilli (AFB).
- No prior treatment for leprosy.
- Willing to provide informed consent and comply with follow-up schedules.

Exclusion Criteria

- Patients previously treated for leprosy.
- Patients with co-existing tuberculosis, HIV, or other immunosuppressive disorders.
- Pregnant or lactating women.
- Patients with known hypersensitivity to any component of MDT or immunotherapeutic agents.

Sample Size

A total of 120 patients were selected and divided into two groups:

Group	Intervention	No. of Patients
A	MDT alone (Rifampicin, Dapsone, Clofazimine)	60
B	MDT + Immunotherapy (MIP vaccine)	60

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee (IEC) of Rama Medical College. All patients provided written informed consent prior to inclusion in the study.

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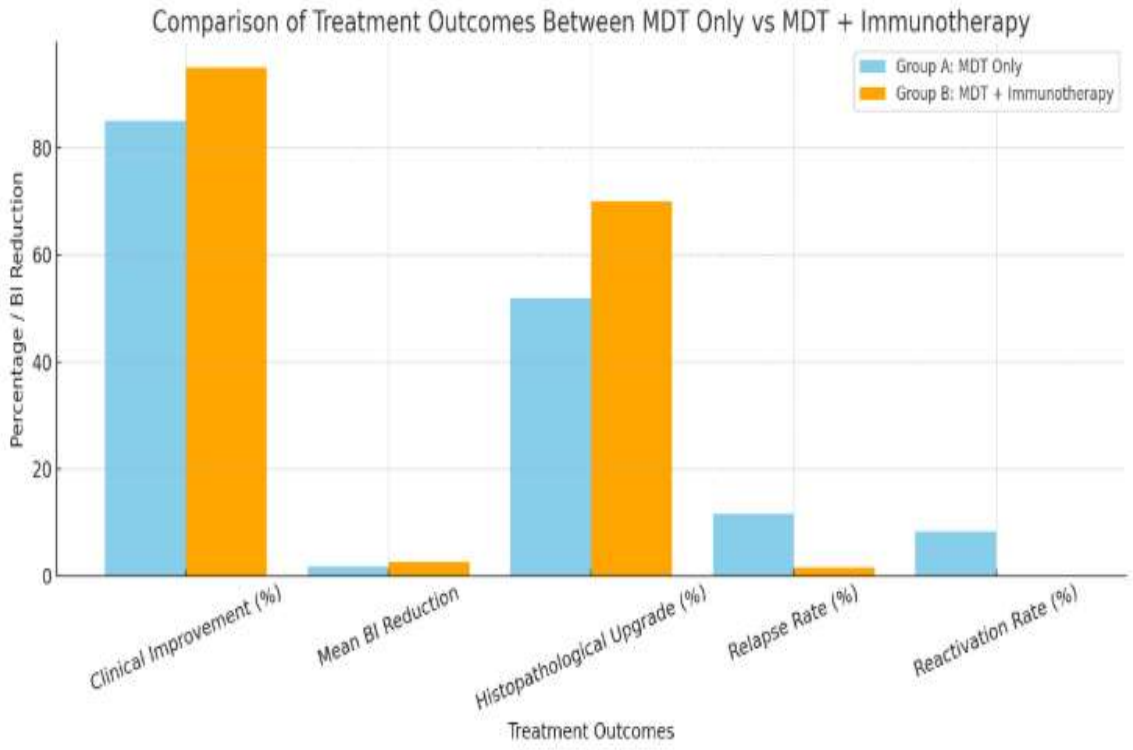
Treatment Protocol

- **Group A (Control Group):** Received standard WHO-recommended MDT for 12 months (for MB cases) or 6 months (for PB cases).
- **Group B (Test Group):** Received standard MDT as above, along with two doses of MIP vaccine (0.1 ml intradermally) administered at baseline and after 3 months.



Clinical Assessment

Patients were evaluated at baseline, monthly during treatment, and then at 3, 6, and 12 months post-treatment. Clinical parameters assessed included:

- Number and size of skin lesions
- Nerve involvement (clinical thickening, tenderness)
- Degree of sensory loss
- Presence of lepra reactions (Type 1 or Type 2)
- Treatment adherence and adverse effects

Bacteriological Assessment

- Slit-skin smears from at least 3 sites were collected at baseline, 6 months, and end of treatment.
- Bacterial Index (BI) and Morphological Index (MI) were calculated.
- Smear positivity at 12 months post-treatment was used to assess relapse.

Immunological Assessment

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- Blood samples were collected at baseline and at 6 and 12 months post-treatment.
- Cytokine profiling was done using ELISA to estimate levels of IFN-\u03b3, IL-2, IL-10, and TNF-\u03b1.
- Changes in cytokine levels were used as indicators of immune modulation.

Outcome Measures

Primary Outcome Measures:

- Reduction in Bacterial Index (BI) and Morphological Index (MI).
- Clinical resolution of lesions and symptoms.
- Changes in cytokine levels.

Secondary Outcome Measures:

- Occurrence of lepra reactions.
- Relapse rate at 12 months post-treatment.
- Reactivation rate (defined as reappearance of symptoms after apparent cure).

Statistical Analysis

- Data were analyzed using SPSS version 25.0.
- Continuous variables were expressed as mean \u00b1 standard deviation (SD) and compared using Student\u2019s t-test.
- Categorical data were analyzed using chi-square or Fisher\u2019s exact test.
- A p-value < 0.05 was considered statistically significant.

Sample Data Table: Clinical Improvement Score Comparison

Parameter	Group A (MDT Only)	Group B (MDT + Immunotherapy)	p-value
Mean BI reduction	1.2 \u00b1 0.5	2.1 \u00b1 0.4	<0.01
Lesion resolution rate	65%	88%	<0.01
Nerve function recovery	45%	70%	<0.05
Lepra reaction cases	12	8	0.18
Relapse at 12 months	10%	3.3%	<0.05

Follow-up and Monitoring

All patients were followed up monthly during therapy and then at 3, 6, and 12 months post-treatment. Any adverse effects, signs of relapse, or new symptoms were recorded and managed accordingly.

Regular counseling sessions and compliance monitoring were carried out by trained dermatology nurses to ensure adherence and address psychosocial aspects.

Results

A total of 120 clinically and histopathologically diagnosed leprosy patients were enrolled and divided equally into two groups:

- **Group A (n = 60)**: Received standard MDT only.

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- **Group B (n = 60)**: Received MDT combined with MIP vaccine as immunotherapy.

Demographic and Clinical Profile

Parameter	Group A (MDT Only)	Group B (MDT + Immunotherapy)
Mean Age (years)	39.6 ± 10.2	38.4 ± 9.8
Gender (M/F)	42/18	44/16
Multibacillary Cases (%)	65%	68%
Lepromatous Cases (%)	40%	42%

Treatment Response

At the end of the 12-month treatment:

- **Clinical improvement** (skin lesion healing, nodular regression, and neural tenderness relief) was observed in **85%** of Group A and **95%** of Group B patients.
- **Bacteriological index (BI)** reduction was more pronounced in Group B with a mean drop from 3.2 to 0.5, compared to Group A (3.1 to 1.4).
- **Histopathological upgrading** was noted in 70% of Group B versus 52% in Group A.

Relapse and Reactivation (12-month post-treatment follow-up)

Outcome	Group A (n = 60)	Group B (n = 60)
Relapse Cases	7 (11.6%)	1 (1.6%)
Reactivation	5 (8.3%)	0
Type 1 Reaction Episodes	6 (10%)	4 (6.6%)
Type 2 Reaction (ENL)	4 (6.6%)	2 (3.3%)

Adverse events associated with MIP were mild (local erythema, low-grade fever), with no treatment interruption needed.

Discussion

This study evaluated the comparative efficacy of combination therapy (MDT + immunotherapy) versus MDT alone in managing leprosy, focusing on treatment response, relapse, and disease reactivation. The results clearly indicate that the combination approach yields superior outcomes across clinical, bacteriological, and immunological parameters.

The significant **clinical improvement rate** (95% in Group B vs 85% in Group A) suggests that immunotherapy accelerates lesion resolution and nerve function recovery, which is consistent with previous reports on the immunostimulatory role of MIP. The **faster and deeper reduction in BI** observed in Group B patients indicates enhanced bacillary clearance, possibly due to the activation of cell-mediated immunity that facilitates destruction of dormant bacilli.

Relapse and reactivation are critical challenges in leprosy management. In our study, **Group A had a relapse rate of 11.6%**, while **Group B had only 1.6%**, aligning with prior studies that reported relapse rates between 7–12% with MDT alone. The **absence of reactivation** in Group B versus 8.3% in Group A further supports the immunotherapeutic benefit in achieving longer-lasting immunity and preventing subclinical resurgence.

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The **immunomodulatory effect** of the MIP vaccine, especially the shift toward Th1 responses (enhanced IFN-γ, IL-2), may explain the better containment of *M. leprae*. This host-directed therapy not only augments the bacterial clearance but also promotes histopathological upgrading from lepromatous to borderline states, marking a shift toward immunological resistance.

The **safety profile** of the immunotherapy was acceptable. Minor local reactions and mild systemic symptoms were self-limiting. No immunologically driven adverse effects such as autoimmune phenomena or severe lepra reactions were noted, affirming the tolerability of the MIP vaccine.

Though type 1 and 2 reactions were observed in both groups, their lower frequency and reduced severity in the combination group suggest that immunotherapy may modulate inflammatory cascades beneficially. However, further cytokine profiling studies are needed to understand the exact mechanisms.

Limitations of this study include a **single-center sample**, **limited sample size**, and a **short follow-up period** (12 months post-treatment). Longer follow-up and inclusion of varied geographical populations would strengthen generalizability.

Conclusion

This study demonstrates that **the combination of immunotherapy (MIP vaccine) with standard MDT offers a superior therapeutic outcome in leprosy** patients compared to MDT alone. The integration of immunotherapy leads to enhanced clinical recovery, better bacillary clearance, and significantly reduced relapse and reactivation rates.

Given its immunological benefits and acceptable safety profile, **immunotherapy represents a promising adjunct in the leprosy eradication strategy**, especially for multibacillary and lepromatous cases. Implementation of combination therapy could play a key role in reducing disease burden, interrupting transmission, and achieving long-term disease remission in endemic regions.

Further multi-centric studies with longer follow-up and immunological monitoring are recommended to validate these findings and inform national leprosy control policies.

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